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Apnea of prematurity: when is the right time to stimulate?

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Apnea of prematurity (AOP) remains one of the common diagnoses in neonatal intensive care units, especially with the increased survival of extremely premature infants. Multiple definitions exist for AOP, depending on the medical society. It has been defined by the American Academy of Pediatrics Committee of the Fetus and Newborn as the presence of respiratory pauses for more than 20 s or shorter pauses associated with cyanosis or desaturations or bradycardia less than 100 bpm in infants less than 37 weeks gestational age.[1] The control of breathing is a complex process, which includes interaction between multiple peripheral and central receptors, neurons, and the respiratory center in the bulbo-pontine region, which is responsible for rhythmogenesis. AOP is the best single indicator of the immaturity of this process.[2] An increasing number of apnea days has previously been shown to be associated with worse clinical outcomes, including abnormal neurodevelopment, which might be related to intermittent hypoxic episodes and bradycardia during those events.

Methylxanthines and non-invasive respiratory support have been the mainstays of the management of AOP. Caffeine citrate is the only Food and Drug Administration-approved medication for the treatment of AOP. However, despite these interventions, the severity of AOP can progress to needing invasive mechanical ventilation and its untoward consequences. In most cases, sensory tactile stimulation, in addition to supplemental oxygen, terminates the episode. The mechanism by which tactile stimulation stimulates respiration is unclear, but it is postulated that it does so by producing non-specific excitatory neuronal impulses that result in respiratory stimulation together with activating the reticular formation of the brain stem, leading to arousal.[3] In addition, limb motion has been shown to increase respiratory rates even during sleep through proprioceptive afferents, which coordinate respiratory generation and locomotion.[4] Moreover, the effect of mechanical stimulation on the respiratory centers depends on the nerves that are stimulated. Various sensory receptors are present throughout the skin, each type responding to a different degree of stimulus, indicating that the location and degree of tactile stimulus can lead to a different response.[5,6]

Despite multiple studies evaluating the role of tactile stimulation in managing AOP, many questions still need to be answered. One such question is whether the timing of stimulation matters in preventing and mitigating AOP. Cramer and colleagues[7] tried to answer the question in this journal issue. Cramer's study is the first preclinical study that investigated the impact of timing of stimulation on AOP prevention and progression. The investigators used a custom-made mechanical stimulation device to administer mechanical vibrotactile stimulation to determine whether anticipatory stimulation was more beneficial than reactive stimulation. The study utilized preterm rabbit kittens exposed to hypoxia as a model and compared the effects of mechanical vibrotactile stimulation administered either in anticipation of apnea at the onset of irregular breathing (IB) or reactively upon the onset of apnea. The anticipatory approach involved delivering stimulation when IB was anticipated, whereas the reactive approach involved stimulation only upon the occurrence of apnea. Various physiological parameters were measured, including breathing rate, heart rate, and lung functional residual capacity, alongside the occurrence and duration of apnea episodes. The anticipatory stimulation approach significantly reduced the incidence and duration of apnea compared to the reactive approach. Additionally, kittens in the anticipatory group exhibited higher breathing rates and lower variability in inter-breath intervals, suggesting improved cardiorespiratory stability. The study highlights the importance of timing in the effectiveness of tactile stimulation, providing new evidence that intervening before the onset of apnea is more beneficial than reactive stimulation once the apnea is established. Previously, the site, the type, and the intensity of the stimuli were shown to be important regarding the response to stimulation[8]; this study proves that timing is also essential.

Major strengths of this study include the innovative design and setup of the vibrotactile stimulation device, in addition to the comprehensive collection of data points that support their conclusion. Further, the investigators used preterm rabbit kittens as young as 29 days gestation, increasing the translational potential of the study. Despite these strengths, there is room for improvement. Since around 20% of the kittens in the reactive group did not progress to have apnea, the question remains if the IB induced by hypoxemia was severe enough to evaluate the comprehensive beneficial effect of anticipatory stimulation. Further, using different stimulatory amplitudes between the two groups added another variable to the experiment that could have affected how each group reacted to the stimuli.

In theory, developing a system for tactile stimulation for AOP prevention could be more beneficial than a system for AOP treatment. However, sensory stimulation might be associated with a disturbance in the sleep rhythm of the neonate and is usually associated with a delay in response time.[9,10] Therefore, anticipatory tactile stimulation for AOP can be cost-effective if used in conjunction with precise predictive models of the disease. The preventive strategy also has the potential to decrease the exposure of preterm infants to respiratory stimulants. However,

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further research is warranted to refine and validate these findings, particularly in clinical settings, before widespread implementation.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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